PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tatsuki SHIOTA, et al.

Appln. No.: 10/031,698

Confirmation No.: 8252

Filed: January 23, 2002

For: CYCLIC AMINE CCR3 ANTAGONIST

Docket No: Q68142

Group Art Unit: 1617

Examiner: Shengjun WANG

SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Per the second full paragraph at page 8 of the Reply filed October 26, 2008, submitted herewith is a copy of an executed Declaration Under 37 C.F.R. §1.132 signed by Tatsuki Shiota.

In the declaration, the Declarant explains that the compounds of the present invention are not taught or suggested by the compounds of Rogers et al., because the removal of one -CH_2- group from a carbon chain changes the shape of the molecule, such that one of ordinary skill in the art would not expect the modified compounds to retain the activity of the original compounds. Thus, the Declarant concludes that it is unexpected and surprising that the compounds of the present invention actually show potent CCR3 inhibitory activity.

Entry and consideration of this Declaration are requested, respectfully.

Respectfully submitted,

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DECLARATION UNDER 37 C.F. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Tatsuki Shiota, c/o TEIJIN PHARMA LIMITED, Pharmaceutical Discovery Division, Pharmaceutical Planning Department, 4-3-2 Asahigaoka, Hino, Tokyo 191-8512, Japan, do hereby declare:

That I am by profession a research scientist having earned a Ph.D. degree in organic chemistry from Osaka University in March 1989;

That I have been employed by TEIJIN PHARMA LIMITED, Tokyo, Japan, since April 1989;

That I have been engaged in pharmaceutical discovery research as a medicinal and organic chemist, then a manager of patent strategy section, in the same company to date;

That I am fully familiar with the pertinent art of the above-identified U.S. application (hereinafter referred to as "present application" for brevity) as an inventor;

That, to show that the present invention should be patentable, I provide the following explanations.

I would like to explain that the compounds of the present invention should not be considered taught or suggested by the compounds of Rogers et al.

Applicant of the present application amended claim 7 to recite that "n" is 0. In contrast, the compounds of Rogers et al. are all 3-methylpyrrolidines. Therefore, a fundamental difference between them is the existence or nonexistence of a CH_2 (methylene) group.

In the field of medicinal chemistry, "bioisosterism" and "bioisoster" are well known as useful and primary concept. For instance, in one of the most familiar books in the field, "Burger's Medicinal Chemistry and Drug Discovery", classic bioisosters are illustrated (M. E. Wolff Ed., *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., vol. 1: Principles and Practice, John Willey & Sons, New York, 1995, p. 786, Table 19.1), and it teaches that bioisosters of CH_2 group as a bivalent group are "-O-", "-S-", "-Se-", and "-NH-". In the concept of bioisosterism, it is important to keep the number of valence electrons, the length, and direction or angle of a group or atom. Additionally, medicinal chemists also know that the removal of one $-CH_2-$ from a carbon chain (an alkylene group) changes its length and direction, and, especially, the direction of the chain. In other words, the shape of the molecule would change significantly, although their 2-dimensional structures are likely to be similar.

For these reasons, I believe that retention of activity of a compound after the removal of CH_2 group is not expected. It is unexpected and surprising results that the compounds of the present invention, actually show the potent CCR3 inhibitory activity despite that a CH_2 group was removed from the compound structure of Rogers et al, and it is quite inventive.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 17th day of Jan ,2008

Tatsuki Shiota

BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

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Edited by

Manfred E. Wolff

ImmunoPharmaceutics, Inc.
San Diego, California

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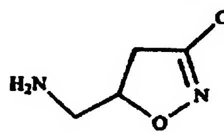
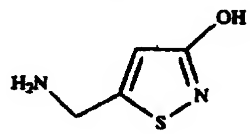
Categories of classic isosteres have been illustrated (2) (Table 19.1).

Dihydromuscimol 1 and thiomuscimol 2 are cyclic analogs of γ-aminobutyric acid (GABA) in which the C=N moiety of the heterocyclic ring is bioisosteric with the C=O of GABA. In addition, the -S- moiety of thiomuscimol is bioisosteric with the ring -O- of dihydromuscimol. Both structures (1) and (2) are highly potent agonists at GABA-A receptors (3). A classic bioisosteric replacement study was reported for a methoxytetrahydropyran-derived inhibitor (4) of 5-lipoxygenase (4) (Table 19.2). None of the isosteric replacements was as potent as the lead compound (4). However, the thio isostere (5) approaches the oxygen compound (4) in potency, and



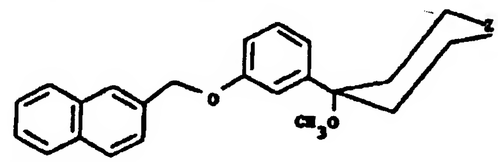
(1)



(2)

(3)

Table 19.2 Inhibition of 5-Lipoxygenase



Structure	Z	IC_{50} (μM)
(4)	O	0.07
(5)	S	0.4
(6)	CH_2	2.6
(7)	C=O	3.4
(8)	SO	4.2
(9)	SO_2	10.6
(10)	NCH_3	>40

Table 19.1 Bioisosteric Atoms and Groups

1. *Univalent*

–F	–OH	$-NH_2$	$-CH_3$	–Cl
		–SH	PH_2	
		–I	t-C_4H_9	
		–Br	$-i-C_3H_7$	

2. *Bivalent*

–O– COOR –S– COSR –Se– $COCH_2R$ $-CH_2-$ –NH– CONHR

3. *Tervalent*

–N=	–CH=
–P=	–As=

4. *Quadrivalent*

$-\overset{|}{\underset{|}{\mathrm{C}}}-$ $-\overset{|}{\underset{|}{\mathrm{Si}}}-$

5. *Ring equivalents*

–CH=CH– –S– (e.g., benzene-thiophene)

=CH– =N– (e.g., benzene-pyridine)

–O– –S– $-CH_2-$ –NH–